論 文 の 内 容 の 要 旨

論文題目　Selective control of up-regulated and down-regulated genes by temporal patterns and doses of insulin
（インスリン刺激の時間パターンと濃度による選択的遺伝子発現制御）

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Secretion of insulin transiently increases after eating, resulting in a high circulating concentration. Fasting limits insulin secretion, resulting in a low concentration of insulin in the circulation. We analyzed transcriptional responses to different temporal patterns and doses of insulin in the hepatoma FAO cells and identified 13 up-regulated and 16 down-regulated insulin-responsive genes (IRGs). The up-regulated IRGs responded more rapidly than did the down-regulated IRGs to transient stepwise or pulsatile increases in insulin concentration, whereas the downregulated IRGs were repressed at lower concentrations of insulin than those required to stimulate the up-regulated IRGs. Mathematical modeling of the insulin response as two stages—(i) insulin signaling to transcription and (ii) transcription and mRNA stability—indicated that the first stage was the more rapid stage for the down-regulated IRGs, whereas the second stage of transcription was the more rapid stage for the up-regulated IRGs. A subset of the IRGs that were up-regulated or down-regulated in the FAO cells was similarly regulated in the livers of rats injected with a single dose of insulin. Thus, not only can cells respond to insulin but they can also interpret the intensity and pattern of signal to produce distinct transcriptional responses. These results provide insight that may be useful in treating obesity and type 2 diabetes associated with aberrant insulin production or tissue responsiveness.

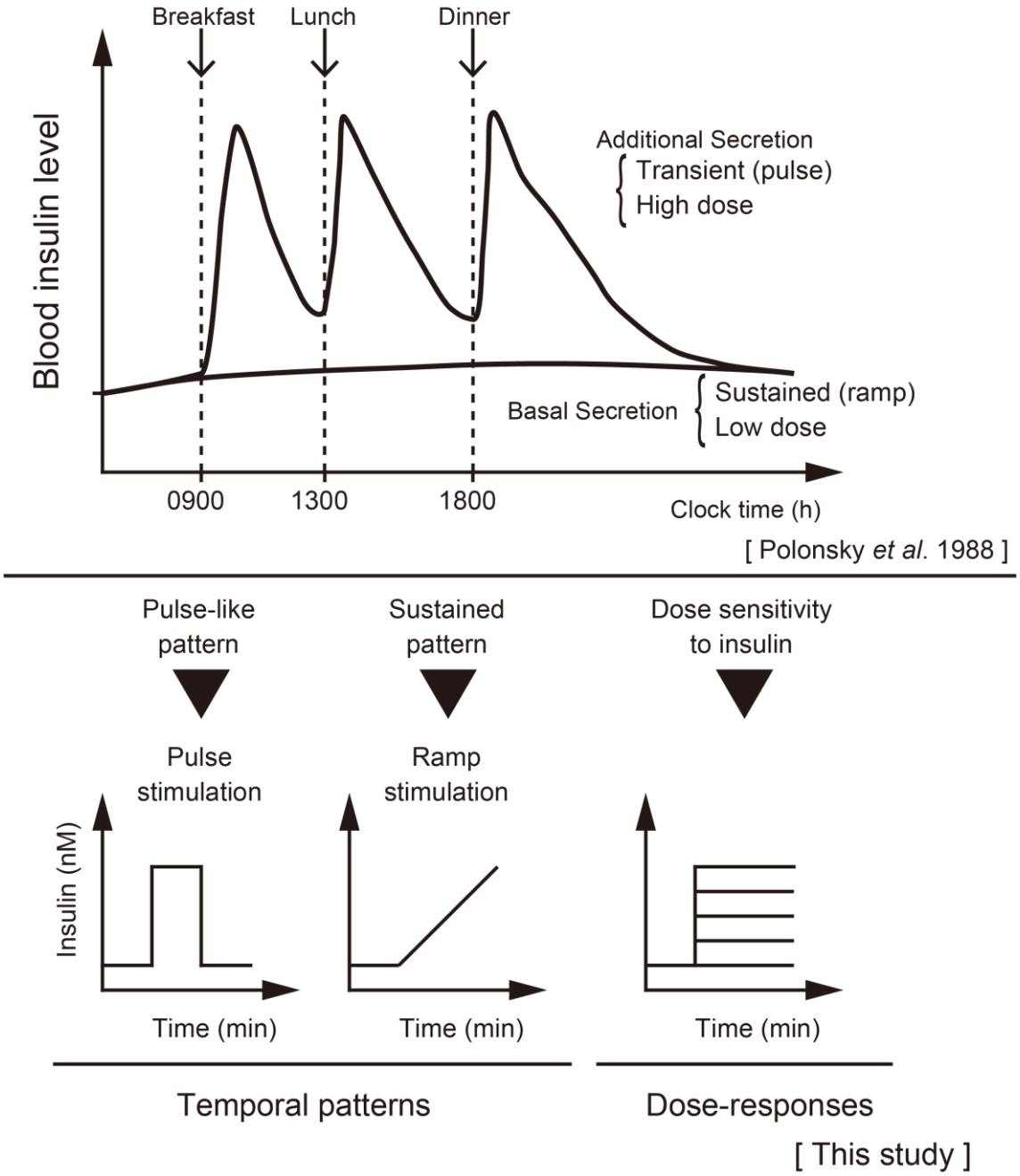

Figure 1. Experimental design of insulin stimulation patterns based on *in vivo* temporal patterns of blood insulin. The additional insulin secretion is characterized by the pulse-like transient increase with a high dose (approximately on the order of nM with a duration of approximately 3 h), and the basal secretion is characterized by the ramp-like sustained increase with a low dose (approximately on the order of tens pM with a duration of approximately 10 h [overnight fasting]). Based on in vivo temporal patterns of insulin, we designed the pulse stimulation and high doses of insulin and the ramp stimulation and low doses, which resemble additional and basal secretion of insulin, respectively.

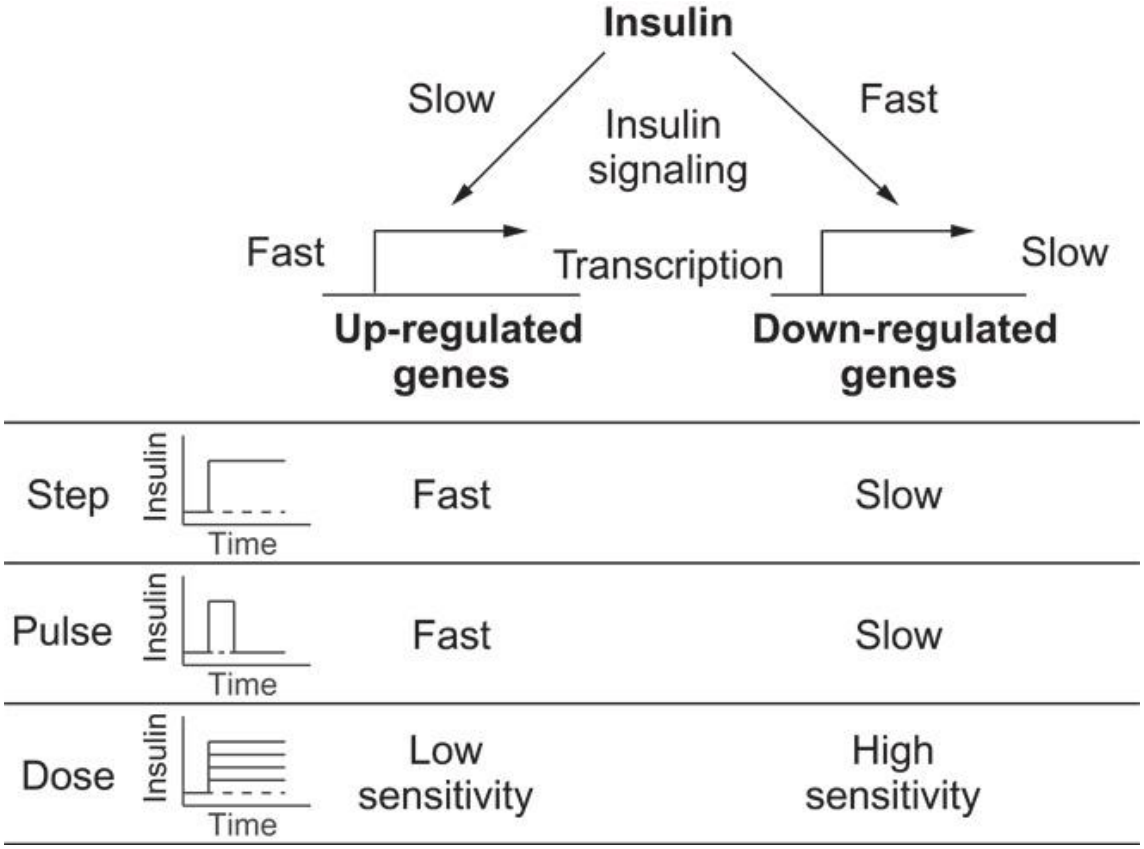

Figure 2. Selective control of the up-regulated IRGs and down-regulated IRGs by temporal patterns and doses of insulin. Mathematical modeling revealed that insulin signaling of the down-regulated IRGs is more rapid than that of the up-regulated IRGs, whereas transcription of the up-regulated IRGs is more rapid than that of the down-regulated IRGs. In experiments, the up-regulated IRGs responded more rapidly to step and pulse insulin stimulation, whereas the down-regulated IRGs showed higher sensitivity than did the up-regulated IRGs to insulin doses.